

REMARKS

I. The Invention

The present invention relates to a fibrinogen-based tissue adhesive. Prior to this invention, fibrinogen-based tissue adhesives generally include an inhibitor of plasminogen activator or an inhibitor of plasmin (*e.g.*, aprotinin), since plasmin is known to cause premature fibrinolysis, which can severely compromise the effectiveness of a tissue adhesive. The tissue adhesive of the present invention comprises an elastase inhibitor (*e.g.*, eglin) and is formulated based on the surprising discovery that non-plasminogen fibrinolysis inhibitors, or the so-called "elastase inhibitors," can inhibit fibrinolysis in a manner equally effective to fibrinolysis inhibition mediated by known inhibitors of plasmin or plasminogen activator.

II. Status of the Claims

Claims 1-28 were initially filed, and claims 29-73 were later added. Claims 1-28, 30-32, 34, 35, 43-50, 52, 53, and 61-69 have been canceled, whereas claims 29, 33, 36-42, 51, 54-60, and 70-73 remain pending.

III. Claim Rejection

35 U.S.C. §103

Claims 29, 33, 36-42, 51, 54-60, and 70-73 stand rejected under 35 U.S.C. §103(a) for alleged obviousness over Hammarstrom or Wadstrom in view of Robertson *et al.* or WO 92/22309 and further in view of Akinson *et al.* Applicants respectfully traverse the rejection.

First, Applicants believe that a *prima facie* case of obviousness is yet to be made. In order to establish a *prima facie* showing of obviousness, three requirements must be satisfied: all limitations of a pending claim must be expressly or impliedly disclosed by prior art references; there must be a suggestion or motivation in the art for one skilled artisan to combine the limitations; and there must be a reasonable expectation of success in making such a combination. MPEP §2143.

Applicants contend that these references relate to very different areas of the broad concept of "wound healing" and therefore provide neither a suggestion or motivation for one of skill in the art to combine the claim elements nor a reasonable expectation of success in combining the elements. As Applicants have previously pointed out, Hammarstrom discloses a tissue adhesive used for joining living mineralized tissue, such as teeth or bones, or for facilitating introduction of artificial implants, such as tooth implants and artificial joints. Wadstrom describes a tissue adhesive comprising fibrin or fibrinogen and a polymer for a desirable viscosity and reduced scar formation during wound healing. The reference further describes the use of the composition as a sealant in soft tissues such as blood vessels and liver. Robertson relates to a methods and compositions useful for preventing and treating corneal haze caused by exposure to laser irradiation during eye surgery. The use of elastase inhibitors as "epithelial cell health promoters" is suggested to enhance the overall health of the eye. WO 92/22309 describes therapeutic agents comprising an elastase inhibitor, 4-(4-chlorophenylsulphonylcarbamoyl)benzoyl-L-valyl-L-proline 1(RS)-(1-trifluoroacetyl-2-methylpropyl)amide, for the treatment and prevention of certain vascular diseases and conditions (such as myocardial ischemia and stroke) in which neutrophils are involved or implicated. Akinson teaches eglin as an inhibitor of elastase and does not directly relate to wound healing of any type.

"Wound healing" is a term loosely used to describe a broad spectrum of healing processes of highly diverse nature. A quick PubMed search of literature using this term at the NCBI web site reveals a large assortment of publications relating to the healing of a variety of injured tissues such as bones, joints, teeth, tendons, cartilages, internal organs (*e.g.*, liver, lungs and airway, heart, gastrointestinal tract, and the nervous system), muscles, skin, cornea, *etc.*, as well as wounds caused by different reasons (*e.g.*, an external force and/or a pathological condition). *See, e.g.*, abstracts of some exemplary publications, attached as Exhibit A. Because of the term "wound healing" encompasses such a wide variety of conditions involving every tissue type in a human body, very different treatment methods are necessary to address the different healing mechanisms, which are determined by the distinct physiology of each tissue type. The cited references describe very different types of tissue injuries: fractured

bones/dislodged teeth in Hammarstrom, trauma to soft tissues in Wadstrom, laser injury of cornea in Robertson, and vascular diseases involving abnormal neutrophil activity in WO 92/22309. The Examiner has not pointed out where in the cited references one of skill in the art would find a motivation or suggestion to combine the elements of the pending claims in this application.

In fact, Applicants believe that the drastic difference in the nature of the wounds (*e.g.*, tissue type, cause, *etc.*) described in the references tends to teach an artisan away from combining the elements, as the artisan would certainly recognize the need of different treatment methods for healing the different types of wounds. One particular example of such teaching away is found in WO 92/22309. This reference teaches the use of an elastase inhibitor-containing composition for treating neutrophil-related vascular disease. On page 4, in the first and second full paragraphs, it is stated that such composition may further include a thrombolytic agent, such as a plasminogen activator. It is well known that for a tissue adhesive to function properly, premature fibrinolysis should be suppressed. The inclusion of a plasminogen activator (which turns plasminogen into plasmin, which in turn causes fibrinolysis) as suggested by WO 92/22309 would therefore severely undermine the effectiveness of a tissue adhesive, if not rendering the adhesive completely useless.

Moreover, even if a motivation or suggestion to combine the claim elements could somehow be found in the cited references, Applicants contend that there still would be no reasonable expectation of success in combining the elements and obtaining an effective tissue adhesive. As stated above, the cited references relate to different types of wound healing processes that are determined by different physiological characteristics of the injured tissues as well as the cause of the injuries. When combining the ingredients of different compositions useful in "wound healing" involving very different tissue types and injury conditions, there simply can be no reasonable expectation to achieve a tissue adhesive with a desired level of effectiveness.

Even if *prima facie* obviousness had been properly established, Applicants contend that the claimed elastase-containing tissue adhesive demonstrates unexpected

effectiveness that such unexpected results would be sufficient to rebut the *prima facie* case of obviousness. The unexpected effectiveness of a tissue adhesive comprising eglin or $\alpha 1$ -antiprotease is shown in the examples and figures of the specification.

For instance, Example 1 (beginning on page 17 of the specification) demonstrates the effectiveness of eglin or $\alpha 1$ -antiprotease in blocking fibrinolysis of a tissue adhesive clot in an *in vitro* assay. The results of Example 1 are shown in Figures 1 and 2. In Figure 1, the vertical axis indicates the amount of tissue adhesive clot, where a lower value indicates less fibrinolysis inhibition. The filled bars, unfilled bars, and horizontal line-filled bars indicate the amount of clot present at time points of 0, 7.5, and 15 hours, respectively. As Figure 1 clearly indicates, when there is neither aprotinin (a plasmin inhibitor) nor $\alpha 1$ -antiprotease (an elastase inhibitor) present in a fibrin adhesive (FA), fibrinolysis occurs at 7.5 hours and is significant at 15 hours (first group of bars from the left); when there is aprotinin (1000 U/ml) present in the FA, some protection against fibrinolysis is achieved at 7.5 and 15 hours (second group of bars from the left); when there is $\alpha 1$ -antiprotease (0.01 U/ml) present in the FA, fibrinolysis is essentially completely blocked for at least 15 hours (the third group of bars from the left); and when there is a lower level of $\alpha 1$ -antiprotease (0.001 or 0.0001 U/ml) present in the FA, protection against fibrinolysis is comparable to that achieved by using aprotinin at 1000 U/ml (the fourth and fifth groups of bars from the left). Similarly, Figure 2 shows that the presence of eglin (at 1 ug/ml) in the FA (the middle group of bars) provides nearly complete protection against fibrinolysis for at least 15 hours, superior to the protection by FA alone (the group of bars on the right) or FA containing plasmin inhibitor aprotinin (the group of bars on the left). These results therefore demonstrate an unexpected effectiveness of eglin and $\alpha 1$ -antiprotease in inhibiting fibrinolysis compared to the inhibition by plasmin inhibitor aprotinin, which is traditionally used in the art.

The results of Example 2, which are illustrated in Figures 3 and 4, indicate the effectiveness of eglin for inhibiting fibrinolysis *in vivo*. In Figure 3, the vertical axis indicates the amount of blood loss after the use of tissue adhesive STIM3, which reflects the level of fibrinolysis and a lower value thus indicates more fibrinolysis inhibition. The diagonal line-

filled bars, unfilled bars, and horizontal line-filled bars indicate average blood loss in the group of animals treated with STIM3 with aprotinin, STIM3 without aprotinin, and STIM3 with eglin but without aprotinin, respectively. The results in Figure 3 indicate that while the presence of aprotinin alone in STIM3 can significantly reduce fibrinolysis for at least 2 hours, the presence of eglin alone in STIM3 can also achieve inhibition of fibrinolysis at a comparable level in the same time period. Figure 4 illustrates in a similar fashion that, during a period of 4 hours, the presence of eglin alone in a tissue adhesive can achieve fibrinolysis inhibition at a level comparable with the inhibition by aprotinin, a plasmin inhibitor traditionally used for this purpose. Thus, these *in vivo* data further show that an elastase inhibitor can prevent fibrinolysis at least as effectively as a traditionally used plasmin inhibitors.

The Examiner previously stated that the examples, including the figures, show no fibrinolysis-inhibitory effect provided by the claimed ingredient eglin or $\alpha 1$ -antiprotease (the Advisory Action mailed August 18, 2004). In the Office Action mailed June 30, 2004, the Examiner further asserted that Figures 3 and 4 show best results when eglin is not present (the last paragraph on page 3) of and Applicants do not agree with the Examiner's interpretation of the examples and figures. As discussed above, Figures 1 and 2 show that in an *in vitro* assay, when eglin or $\alpha 1$ -antiprotease is used in a tissue adhesive in place of aprotinin, a higher level of fibrinolysis inhibition can be achieved, superior effectiveness has been demonstrated. Figures 3 and 4 show that in an *in vivo* assay, when eglin is used in place of aprotinin in a tissue adhesive, a comparable level of fibrinolysis inhibition can be achieved. This conclusion is reached by comparing the diagonal line-filled bars, which indicate a tissue adhesive with aprotinin but without eglin; the horizontal line-filled bars, which indicate a tissue adhesive with eglin but without aprotinin; and the unfilled bars, which indicate a tissue adhesive without aprotinin or eglin. Since the results in Figures 3 and 4 show that aprotinin, a well known plasmin inhibitor traditionally used for preventing fibrinolysis in tissue adhesives, can be adequately replaced by a non-plasmin inhibitor previously unknown for this use, Applicants submit that the results are surprising and the effectiveness of the non-plasmin inhibitor so demonstrated is unexpected. In

stating that the best results are achieved when eglin is not present, the Examiner has apparently mistaken the higher values in Figures 3 and 4 to mean better results.

In addition, earlier reports indicate that the non-plasmin fibrinolytic pathway cannot be inhibited by specific elastase-inhibiting peptides, *see, e.g.*, Simon *et al.*, 1993, *Blood* 82:241-4-2422 (cited in the International search report for PCT/AT98/00202). The effectiveness of eglin and $\alpha 1$ -antiprotease to inhibit fibrinolysis of a tissue adhesive as shown in the present application is an unexpected result particularly because of these earlier reports.

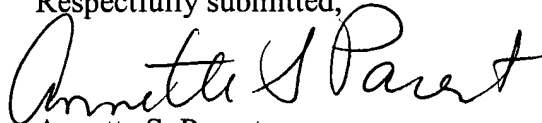
In summary, Applicants contend that no *prima facie* obviousness has been established. Even if a case of *prima facie* obviousness were properly made, Applicants further contend that it would be rebutted by evidence that the claimed tissue adhesive is surprisingly effective, as demonstrated by the experimental data in the present specification. This result is unexpected also because that previous references have reported the inability of specific elastase-inhibiting peptides (*e.g.*, AAPVCK) to block the non-plasmin fibrinolysis. Accordingly, the withdrawal of the obviousness rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

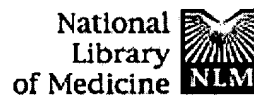
Respectfully submitted,


Annette S. Parent
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Attachments (Exhibit A: abstracts of exemplary references relevant to "wound healing")

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Undisplaced intracapsular hip fractures: results of internal fixation in 375 patients.

Conn KS, Parker MJ.

Department of Trauma and Orthopaedics, Peterborough District Hospital, Peterborough, England, UK.

Three hundred seventy-five patients with an undisplaced intracapsular proximal femoral fracture were treated with internal fixation. Nonunion occurred in 24 patients (6.4%) and avascular necrosis occurred in 15 patients (4.0%). Reoperation with an arthroplasty was required in 29 patients (7.7%). The age, walking ability of the patient, and degree of impaction seen on the anteroposterior radiograph or angulation seen on the lateral radiographs were of statistical significance in predicting fracture healing complications. The results for this series of patients were compared with the results in published reports identified by a comprehensive literature search. Summation of the results indicated that the overall risk of redisplacement or nonunion of the fracture was 4.3% (95% confidence interval, 3.4%-5.3%) with internal fixation of an undisplaced intracapsular fracture. For conservative treatment, the failure rate was 19.6% (95% confidence interval, 17.2%-22.1%). The incidence of avascular necrosis with internal fixation at 1 year was 2.2% (95% confidence interval, 1.6%-2.9%) compared with 2.8% (95% confidence interval, 1.9%-4.0%) with nonoperative treatment. Internal fixation is recommended for the treatment of undisplaced intracapsular hip fractures.

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- Review, Academic

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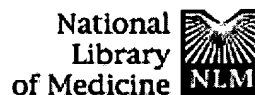
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☐ 1: Plast Reconstr Surg. 2003 Sep;112(3):844-54.

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Is the tendon embryogenesis process resurrected during tendon healing?

Ingraham JM, Hauck RM, Ehrlich HP.

Penn State College of Medicine and Department of Surgery, Milton S. Hershey Medical Center, PA, USA.

The process of embryonic tendon development, including the nature and purpose of collagen fibril segments, is reviewed. It is proposed that tendon fibrillogenesis of repair is related to the fibrillogenesis of tendon embryonic development. The assembly of collagen fibril segment units into longer fibers occurs on the surface of tendon fibroblasts in embryonic tendon development. The biochemist's view of tendon healing, whereby the spontaneous polymerization of tropocollagen monomers regenerates lost tendon collagen fibers, needs to be reconsidered. Furthermore, the importance of direct fibroblast involvement in collagen fiber reassembly during tendon healing needs to be studied in tendon intrinsic regenerative repair.

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- Review
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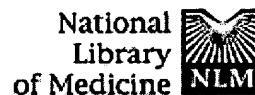
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Repair of full-thickness bowel injury.

Witte MB, Barbul A.

Department of Surgery, University of Tuebingen, Germany.

OBJECTIVE: Colon surgery is more and more often performed in complex situations such as after trauma, under immunosuppression, or in the elderly. Even under optimal conditions, anastomosis fails in certain situations. The objective of this study was to demonstrate the normal phases of bowel healing and to review the local and systemic factors affecting healing with special attention to critical care variables such as major surgery, acute hemorrhage, and infections. **DATA SOURCE:** MEDLINE cited and/or published articles. **DESIGN:** Review analysis. **RESULTS:** Colon healing is a structured cascade of different phases that can be affected by a multitude of local (infection, ischemia) and systemic (diabetes, malnutrition, anemia, hypothermia, trauma) factors. The normal phases of repair, the resulting bursting pressure as an experimental index of healing, and the available published data on local and systemic factors affecting healing are summarized. **CONCLUSION:** Several local and systemic factors negatively affect bowel healing; there is still a small portion of patients who fail to heal, suggesting that intrinsic factors need to be analyzed.

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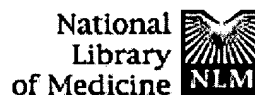
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Mucosal repair in the gastrointestinal tract.

Mammen JM, Matthews JB.

Department of Surgery, University of Cincinnati, Ohio 45367, USA.

OBJECTIVE: The epithelial response to injury in the intestinal mucosa will be described. **DESIGN:** A comprehensive evaluation of the literature was performed to provide a thorough review of mucosal injury and repair. **RESULTS:** The intestinal mucosa is a rapidly proliferating sheet of epithelial cells that sustains injury in response to stresses ranging from physiologic daily digestive trauma to severe insults associated with ischemia, chemicals, and infection. Breaks in epithelial continuity impair mucosal barrier function, perturb normal absorptive and secretory transport properties, and render the host susceptible to local infection and distant organ pathology. Minor breaches are rapidly repaired by epithelial restitution, a process independent of cell proliferation. Restitution is regulated by a variety of cytokines and growth factors and is modulated by integrin-dependent interactions with the extracellular matrix. The intracellular mechanisms that control restitution are complex and involve signaling pathways that control dynamic remodeling of the actin cytoskeleton. Emerging understanding of reparative processes suggest several possible therapeutic strategies to enhance gastrointestinal wound healing. **CONCLUSION:** Minor epithelial injuries are repaired with the complex process of epithelial restitution independent of cell proliferation.

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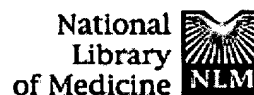
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**Injury and repair in lung and airways.****Shimabukuro DW, Sawa T, Gropper MA.**

University of California, San Francisco, 94143, USA.

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are common causes of morbidity and mortality in the intensive care unit. ALI/ARDS occurs as a result of systemic inflammation, usually triggered by a microorganism. Activation of leukocytes and release of proinflammatory mediators from multiple cellular sources result in both local and distant tissue injury. Tumor necrosis factor-alpha and interleukin-1 beta are the best characterized of the proinflammatory cytokines contributing to ALI/ARDS and subsequent fibrosis. The ultimate clinical course of ALI/ARDS often is determined by the ability of the injured lung to repopulate the alveolar epithelium with functional cells. Death may occur when fibrosis predominates the healing response, as it results in worsening lung compliance and oxygenation. The rodent bleomycin model of lung fibrosis allows the use of molecular tools to dissect the cellular and subcellular processes leading to fibrosis. The elements of this response may provide therapeutic targets for the prevention of this devastating complication of ALI/ARDS.

Publication Types:

- Review
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PMID: 12907882 [PubMed - indexed for MEDLINE]

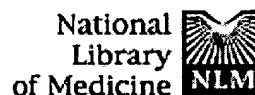
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JRRD**Transplantation strategies to promote repair of the injured spinal cord.****Bunge MB, Pearse DD.**

The Miami Project to Cure Paralysis, Department of Cell Biology, University of Miami School of Medicine, Miami, FL 33101, USA. mbunge@miami.edu

This review describes the results of the transplantation of Schwann cells and olfactory ensheathing glia in combination with other interventions. The complete transection injury model was used to test the combination of Schwann cell bridges with methylprednisolone, neurotrophins, or olfactory ensheathing glia. The contusion injury model was used to compare Schwann cell and olfactory ensheathing glia transplantation and to examine the results of combining Schwann cell transplants with elevated levels of cyclic adenosine monophosphate. The combination strategies were more effective than cell transplantation alone. The improved regeneration response usually involved a reduction in secondary tissue loss, axonal regeneration from brainstem neurons, an increase in myelinated fibers in the transplant, the exit of regenerated fibers from the transplant into the contiguous cord, and an improvement in locomotor function.

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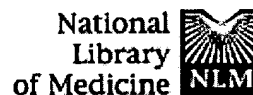
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Management of corneal abrasions.

Wilson SA, Last A.

University of Pittsburgh Medical Center St. Margaret Family Practice Residency Program, Pittsburgh, Pennsylvania 15215, USA. wilsons2@upmc.edu

Corneal abrasions result from cutting, scratching, or abrading the thin, protective, clear coat of the exposed anterior portion of the ocular epithelium. These injuries cause pain, tearing, photophobia, foreign body sensation, and a gritty feeling. Symptoms can be worsened by exposure to light, blinking, and rubbing the injured surface against the inside of the eyelid. Visualizing the cornea under cobalt-blue filtered light after the application of fluorescein can confirm the diagnosis. Most corneal abrasions heal in 24 to 72 hours and rarely progress to corneal erosion or infection. Although eye patching traditionally has been recommended in the treatment of corneal abrasions, multiple well-designed studies show that patching does not help and may hinder healing. Topical mydriatics also are not beneficial. Initial treatment should be symptomatic, consisting of foreign body removal and analgesia with topical nonsteroidal anti-inflammatory drugs or oral analgesics; topical antibiotics also may be used. Corneal abrasions can be avoided through the use of protective eyewear.

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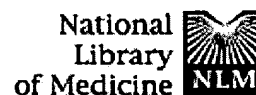
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☐ 1: Clin Orthop. 2004 Jun(423):17-26.

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The role of biomechanics and inflammation in cartilage injury and repair.

Guilak F, Fermor B, Keefe FJ, Kraus VB, Olson SA, Pisetsky DS, Setton LA, Weinberg JB.

Department of Surgery, Duke University Medical Center, Durham, NC, USA.
guilak@duke.edu

Osteoarthritis is a painful and debilitating disease characterized by progressive degenerative changes in the articular cartilage and other joint tissues. Biomechanical factors play a critical role in the initiation and progression of this disease, as evidenced by clinical and animal studies of alterations in the mechanical environment of the joint caused by trauma, joint instability, disuse, or obesity. The onset of these changes after joint injury generally has been termed posttraumatic arthritis and can be accelerated by factors such as a displaced articular fracture. Within this context, there is considerable evidence that interactions between biomechanical factors and proinflammatory mediators are involved in the progression of cartilage degeneration in posttraumatic arthritis. In vivo studies have shown increased concentrations of inflammatory cytokines and mediators in the joint in mechanically induced models of osteoarthritis. In vitro explant studies confirm that mechanical load is a potent regulator of matrix metabolism, cell viability, and the production of proinflammatory mediators such as nitric oxide and prostaglandin E2. Knowledge of the interaction of inflammatory and biomechanical factors in regulating cartilage metabolism would be beneficial to an understanding of the etiopathogenesis of posttraumatic osteoarthritis and in the improvement of therapies for joint injury.

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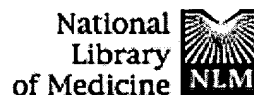
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Joint injury, repair, and remodeling: roles in post-traumatic osteoarthritis.

Buckwalter JA, Brown TD.

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Joint injuries, especially intraarticular fractures, frequently lead to progressive joint degeneration that causes the clinical syndrome of posttraumatic osteoarthritis. Orthopaedists try to prevent this disease by attempting to restore joint congruity, alignment, and stability; however, many patients have crippling joint pain and dysfunction develop despite optimal current treatment. The pathophysiology of posttraumatic osteoarthritis has not been explained. It is not simply the magnitude and type of injury that determines whether an injured articular surface will repair and remodel or undergo progressive degeneration. For these reasons, clinically significant progress in preventing posttraumatic osteoarthritis depends on advances in understanding of the pathogenesis of this disease that will make it possible to decrease the risk of articular surface degeneration and facilitate articular surface repair and remodeling. We examine the relationships between joint injury, repair and remodeling, and joint degeneration; the factors that increase the risk of posttraumatic joint degeneration; and, the questions that need additional investigation to develop treatments of joint injuries that will decrease the risk or severity of posttraumatic osteoarthritis.

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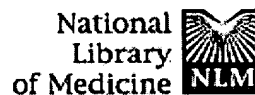
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Management of soft tissue wounds associated with type III open fractures.

Esterhai JL Jr, Queenan J.

Department of Orthopaedic Surgery, Hospital of the University of Pennsylvania, Philadelphia.

The orthopedist's goals are to prevent wound infection, expedite fracture healing, and restore optimal function. The importance of the soft tissue envelope to fracture healing is well recognized. In spite of continual research concerning wound repair, we remain at a loss to define precisely what starts the wound healing process and what ultimately stops it. In this article, we consider the basic science of wound repair, the effects of the patient's nutrition and volume status, soft tissue wound dressing options, soft tissue transfers, and specific recommendations.

Publication Types:

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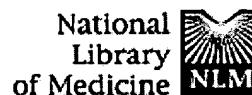
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**ELSEVIER SCIENCE
FULL-TEXT ARTICLE****Protocol for the successful treatment of pressure ulcers.****Brem H, Lyder C.**

Department of Surgery, Columbia University College of Physicians & Surgeons,
5141 Broadway, New York, New York 10034, USA. hb2133@columbia.edu

Bed-bound patients with pressure ulcers are almost twice as likely to die as are those without pressure ulcers. If pressure ulcers are treated with a comprehensive regimen upon early recognition, nearly all stage IV ulcers can be avoided. Furthermore, such a regimen can significantly reduce the comorbidities, mortalities, and costs of treatments resulting from stage IV ulcers. The costs of treatments for comorbidities after the ulcer progresses to stage IV far outweigh the costs for early treatment of the ulcer before it progresses beyond the early stages. We describe herein the 4 stages of pressure ulcers, as well as the pathogenesis, costs, and complications associated with these wounds. A comprehensive 12-step detailed protocol for treatment of pressure ulcers is described; this includes recognizing that every patient with limited mobility is at risk for developing a sacral, ischial, trochanteric, or heel ulcer; daily assessment of the skin; objective measurement of every wound; immediate initiation of a treatment protocol; mechanical debridement of all nonviable tissue; establishment of a moist wound-healing environment; nutritional supplementation for malnourished patients; pressure relief for the wound; elimination of drainage and cellulitis; biological therapy for patients whose wounds fail to respond to more traditional therapies; physical therapy; and palliative care. Availability of the described treatment modalities, in combination with early recognition and regular monitoring, ensures rapid healing and minimizes morbidity, mortality, and costs.

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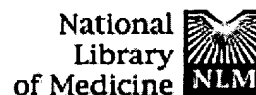
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ELSEVIER SCIENCE
FULL-TEXT ARTICLE

Protocol for treatment of diabetic foot ulcers.

Brem H, Sheehan P, Boulton AJ.

Department of Surgery, Columbia University College of Physicians & Surgeons,
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Each year, 82,000 limb amputations are performed in patients with diabetes mellitus. The majority of these amputations could be avoided by following strict protocols. The collective experience treating patients with neuropathic diabetic foot ulcers of 4 major diabetic foot programs in the United States and Europe were analyzed. The following protocol has been developed for patients with diabetic foot ulcers: (1) measurement of the wound by planimetry; (2) optimal glucose control; (3) surgical debridement of all hyperkeratotic, infected, and nonviable tissue; (4) systemic antibiotics for deep infection, drainage, and cellulitis; (5) offloading; (6) moist-wound environment; and (7) treatment with growth factors and/or cellular therapy if the wound is not healing after 2 weeks with this protocol and a new epithelial layer is not forming. In addition, the pathogenesis of diabetic foot ulcers is discussed, as well as the associated costs and complications, including amputation. Debridement, wound-bed preparation, antibiotics, various types of dressings, biological therapies, growth factors, and offloading are described as treatment modalities for patients with diabetic foot ulcers. In diabetic foot ulcers, availability of the above modalities, in combination with early recognition and comprehensive treatment, ensure rapid healing and minimize morbidity, mortality, and costs, as well as eliminate amputation in the absence of ischemia and osteomyelitis.

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